ORIGINAL ARTICLE

Facilitation of neonatal endotracheal intubation with mivacurium and fentanyl in the neonatal intensive care unit

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Background: Endotracheal intubation in the neonate is painful and is associated with adverse physiological effects. Some premedication regimens have been shown to reduce these effects, but the optimal regimen is not yet determined.
Method: Data on semi-elective intubations were prospectively collected in the neonatal intensive care unit over a six month period. Patients received 20 μg/kg atropine, 200 μg/kg mivacurium (a non-depolarising muscle relaxant) followed by 5 μg/kg fentanyl.
Results: Thirty three patients were electively intubated during this time period. The primary reason for intubation was surfactant administration (53%). Median (range) birth weight, gestational age, and age at intubation were 1360 g (675–4200), 29 weeks (25–38), and 33 hours (1–624) respectively. Twenty two of the infants were intubated on the first attempt. Median duration from initial insertion of the laryngoscope to successful intubation was 60 seconds (15 seconds to 20 minutes). In 18 cases, the first attempt was by a trainee with no previous successful intubation experience, 10 of whom intubated within two attempts. Muscle relaxation occurred at a mean (SD) of 94 (51) seconds, and mean (range) time to return of spontaneous movements was 937 seconds (480–1800). Intubation conditions were scored as excellent using a validated intubation scale.
Conclusion: Effective analgesia can be administered and intubation performed with some brief desaturations, even when junior personnel are being taught their first intubation. In this first report of mivacurium for intubation in the newborn, effective bag and mask ventilation was easily achieved during muscle relaxation and was associated with excellent intubation conditions, permitting a high success rate for inexperienced personnel.

Semi-urgent and elective tracheal intubation is common practice in neonatal intensive care. It is widely recognised to be extremely painful. However, intravenous analgesia before this procedure is not universally used.[1] One survey reported that only 37% of neonatal intensive care units (NICUs) used any form of analgesia or sedation before intubation and less than 8% used a combination of sedation and muscle relaxation.[2] This continues to occur despite consistent evidence to show that conscious awake intubation causes adverse physiological responses.[3] These include profound cardiovascular stress including tachycardia, bradycardia, hypertension and hypotension, pulmonary hypertension, distinct increases in intracranial pressure[4] with a potential increase in intraventricular haemorrhage, and episodes of hypoxaemia associated with gagging, choking, coughing, and laryngospasm.[5] Some premedication regimens have been shown to reduce these side effects, reduce the time taken to intubate, and reduce the number of attempts needed for a successful intubation.[6 7] Concerns raised with premedication include the potential side effects of the various drugs used, difficulty in maintaining an adequate airway after muscle relaxation, and loss of functional residual capacity resulting in hypoxia.[5]

Various different premedication regimens are currently in use.[8] These often include use of an opioid or benzodiazepine alone, an opioid or benzodiazepine in combination with a muscle relaxant (typically suxamethonium), with or without atropine, and, less commonly, barbiturates and ketamine. The optimal regimen remains unknown. We currently use a protocol that consists of atropine, mivacurium (a non-depolarising muscle relaxant), and fentanyl administered in that order before any elective or semi-elective intubation in the NICU. The objective was to document our experience with our current premedication regimen as part of an ongoing neonatal quality improvement initiative. In particular, we wanted to evaluate the success rate of residents with no previous intubation experience, determine the intubation conditions achieved, and evaluate the clinical effects of mivacurium in the neonate including onset and duration of paralysis and any adverse events associated with this premedication protocol.

METHODS

This was a prospective observational study in a level 3 NICU of a teaching hospital. It was part of a quality improvement initiative in the NICU concerning intubation practices. Data was collected by one of two individual personnel on a pro-rata intubation form over a six month period from September 2004 to February 2005. This included information on the patient (birth weight, gestational age, postnatal age at intubation, weight at intubation, and indication for intubation), information about the intubator (healthcare professional, year of training, skill level), the duration of individual attempts, intubation conditions,[9] and the total duration from first attempt to successful intubation. Personnel with at least one previous successful intubation were classified as ''prior experience'' compared with those with no previous successful intubation as ''inexperience''. The duration of each individual attempt was recorded as the time in seconds from insertion of the laryngoscope into the mouth to its removal. The total duration of each successful intubation was from first insertion of the laryngoscope to final successful placement

of the endotracheal tube, again in seconds. This time included each individual intubation attempt and the intervening time periods during which the patient was receiving positive pressure ventilation.

Intubation conditions were assessed using an adapted scoring system (Goldberg scale).[9] A score of one to four is assigned to each of three variables: (*a*) ease of intubation; (*b*) vocal cords; (*c*) response to intubation resulting in a minimum score of three and a maximum score of 12. A score of 3 is excellent, 4–6 good, 7–9 poor, and 10–12 inadequate. A continuous recording and print out of heart rate, respiratory pattern, and oxygen saturation were obtained from the clinically used bedside monitor for each intubation. Adverse events collected were: (*a*) occurrence of desaturation to less than 80%; (*b*) the duration of each desaturation less than 80%; (*c*) lowest saturation; (*d*) bradycardia less than 100.

The onset and duration of paralysis were assessed clinically. Onset of muscle relaxation was determined by absence of spontaneous movements and flaccidity, measured in seconds from the end of the mivacurium administration. Duration of paralysis was determined from onset of paralysis to return of spontaneous movements and preintubation tone.

The intubation protocol consisted of 20 μg/kg atropine followed one minute later by 200 μg/kg mivacurium administered over 15–30 seconds. Fentanyl (5 μg/kg) was then immediately administered over one minute. The patient received positive pressure ventilation with an anaesthesia bag and face mask. Peak pressures administered were assessed by a manometer and adequate chest wall movement and varied depending on the underlying disease process necessitating intubation. A positive end expiratory pressure of 4–5 cm H_2O was typically administered. After preoxygenation to maintain oxygen saturations greater than 95%, the initial intubation was attempted, typically two minutes after fentanyl administration. Each intubation in our unit is nasotracheal with the assistance of an appropriately sized Mcgill forceps. Each attempt was supervised by a neonatology staff member or fellow. No time limit was placed on the intubation attempt, but generally each intubation was aborted when the saturations fell below 80% and successful intubation was not felt to be imminent. Two attempts was the maximum number allowed for inexperienced personnel. The personnel recording the data did not interfere in the intubation process.

Statistical analysis was performed with SPSS for windows version 12 (SPSS Inc, Chicago, Illinois, USA). Comparison between groups was made using *t* tests and χ^2 analysis. $p<0.05$ was considered significant. A linear regression model was used to assess factors related to time of onset of paralysis.

Table 1 Characteristics of patients and intubators, success rates, and clinical effects of mivacurium

Number of patients	33
Birth weight* (g)	1360 (675–4200)
Gestational age* (weeks)	29 (25–38)
Age at intubation* (hours)	33 (1–624)
No previous experience	18
Successful on first attempt	22
Number of attempts	57
Number of attempts/patient	1.72
Onset of muscle relaxation† (seconds)	94 (51)
Return of spontaneous movements†(seconds)	937 (419)

*Median and range.
†Mean (SD).

RESULTS

Fifty patients were intubated semi-electively in the NICU over this time period. Data were recorded prospectively on 33 of these patients during this time period. Detailed data were not collected on the remaining 17 patients because of unavailability of data collectors. The median (range) birth weight, gestational age, and age at intubation were 1360 g (675–4200), 29 weeks (25–38), and 33 hours (1–624) respectively. The intubators consisted of a variety of healthcare professionals. This included residents in paediatrics and obstetrics (predominantly in their first year of training), neonatal nurse practitioners, respiratory technicians, fellows in neonatology, and neonatal staff. In 18 patients, the primary intubator had never successfully intubated previously. Twenty two of the 33 patients were intubated on the initial attempt. The mean number of attempts for the cohort was 1.72 attempts per patient (table 1).

Of the 18 patients for which the primary intubator had no previous experience, 10 were successfully intubated within two attempts (eight on first attempt and two on second). Personnel with prior experience who attempted the primary intubation were successful on their first attempt in 93% of cases. The overall success rate per intubation attempt for inexperienced personnel was 38% compared with 74% for experienced personnel. The mean duration of each attempt was shorter (36 *v* 49 seconds, $p = 0.09$), the mean time to successful intubation was shorter (88 *v* 325 seconds, $p = 0.035$), the number of desaturations to less than 80% were fewer (17 *v* 12, $p = 0.04$) and shorter (21 *v* 14 seconds, $p = 0.1$), and the mean lowest saturation was higher (77% *v* 66%, $p = 0.07$) when the intubator was experienced (table 2).

The mean onset of paralysis was 94 seconds (range 30–240). The mean duration to return of spontaneous movements was 937 seconds (range 480–1800). No patient desaturated to less than 90% from the onset of paralysis to the initial intubation attempt. There was no case of chest wall rigidity. In a linear regression model including gestational age, birth weight, and postnatal age, the onset of paralysis was associated with a higher baseline heart rate ($p = 0.0169$, standard β coefficient -0.51).

DISCUSSION

This is the first reported series on the use of mivacurium for intubation in the newborn in the NICU. Recent surveys have shown that neonatologists are more likely to premedicate now than they were previously.[10 11] However, there is a still a reluctance to use muscle relaxation,[2] which is probably a reflection of the unease with muscle relaxing a patient and then the fear of being unable to intubate. For those who use muscle relaxation, succinylcholine remains the preferred choice, primarily because of its short onset and duration of action. However, there are a number of potential side effects with its use including cardiac arrhythmias, malignant hyperthermia, hyperkalaemia, masseter spasm, fasciculation, and prolonged paralysis.[12]

We currently use mivacurium, a non-depolarising muscle relaxant which is broken down in a similar fashion to succinylcholine by pseudocholinesterase, but is free from the potential serious side effects seen with succinylcholine. Data exist on the onset and duration of action of mivacurium in children and infants,[13] but very few in neonates. We assessed the effects of mivacurium in a wide group of newborns varying in gestational age from 25 to 40 weeks and birth weight 660 to 4200 g. We did not measure train of fours in these subjects because of the inherent difficulties with this technique in this population. We decided to evaluate the clinical effects subjectively, as this should be more representative of clinical practice. We measured the time from administration to onset of action and the overall duration

Table 2 Characteristics of each individual intubation attempt determined by level of experience

	Inexperience	Prior experience	p Value
Number of intubations	26	31	
Success rate (%)	38	74	0.029
Duration of each attempt (seconds)	49 (29)	36 (23)	0.09
Number of desaturations <80%	17	12	0.04
Duration of desaturation (seconds)	21 (38)	14 (35)	0.5
Lowest saturation (%)	66 (22)	77 (20)	0.07
Number of bradycardia <100 beats/min	2	1	0.4

Values are number or mean (SD).

of action. Our findings showed that muscle relaxation occurred at a mean (SD) of 94 (51) seconds. These figures are very similar to a previous publication in infants of 1.5 (0.8) minutes.[13] The onset of muscle relaxation varied from a minimum of 30 seconds to a maximum of 240 seconds. This wide range is similar to that found in older infants and is probably multifactorial related to the variable volume of distribution at the various gestational and postnatal ages of our patients. We were able to show that effective bag and mask ventilation can be easily achieved with a properly fitting facemask and anaesthesia bag in a muscle relaxed patient. This is similar to other published reports of the use of muscle relaxant in neonatology.[4] We maintain a positive end expiratory pressure of 4–5 cm H_2O (measured with a manometer) during the preintubation phase. No patient had a desaturation to less than 90% after muscle relaxation before the initial intubation attempt. The mean duration to return of spontaneous movements was just less than 16 minutes, also very variable, clearance being largely the result of pseudocholinesterase activity, which is variable. This provides adequate time to allow inexperienced personnel a second attempt and also time to secure the endotracheal tube safely after successful placement. Other alternatives such as atracurium and rocuronium have a longer duration of action, which may not be required for most patients.

Fentanyl remains our opiate of choice because of its fast onset of action and relative cardiovascular stability. One of the main concerns with fentanyl use is chest wall rigidity. A number of case reports have documented this problem and case series have estimated the risk at 1.4–4% in the neonatal population.[14 15] The potential for this unwanted effect can be reduced by slow administration of the fentanyl over at least one minute and can be treated with administration of naloxone or muscle relaxants. By using the current protocol (administering the muscle relaxant first followed immediately by fentanyl), we have eliminated this risk despite the use of a dose of fentanyl that is adequate to produce analgesia (5 μg/kg).

Currently no standard criteria exist for certification in neonatal intubation. Falck *et al*[16] have suggested a success rate of 80% to be deemed competent. Konrad *et al*[17] found that success rates for intubation among anaesthetic trainees reached 90% after a mean of 57 procedures. However, these figures are unrealistic in neonatology for a number of reasons. The opportunities for trainees to intubate now are fewer[18] (changes in Neonatal Resuscitation Program (NRP) guidelines for management of meconium stained infants, the use of more non-invasive ventilation, and shorter working hours for junior residents). Various simulations have been developed, but none provide the same conditions as required in daily clinical practice. Therefore, providing optimal conditions in the real life setting may improve the overall success rate while minimising the discomfort to the patient. We assessed intubating conditions using a subjective scoring system, the Goldberg scale.[9] Our protocol provided a median score of 3, which was excellent. This was reflected in an overall success rate of 55% for non-experienced personnel, a high percentage considering none of these people had successfully intubated previously. This figure compares favourably with other studies[16 18] Each resident has completed the NRP before starting the rotation and have practiced intubation skills on mannequins. A muscle relaxed neonate is easier to intubate than a vigorous neonate, and hence we try to achieve optimal conditions before intubation. In the NICU, semi-elective intubations are offered to inexperienced intubators first. They are generally allowed two attempts.

Some fears allied to the use of premedication include an increased risk of hypoxia in the premedicated group.[5] We specifically chose to look at four potential side effects including incidence and duration of hypoxia (oxygen saturation less than 80%), the lowest recorded oxygen saturation, and finally any bradycardia less than 100. The occurrence of these adverse events was very favourable in comparison with previous studies. Pokela and Koivisto,[3] in a randomised trial comparing pethidine with alfentanil and suxamethonium, noted the occurrence of hypoxaemia (defined as a transcutaneous oxygen tension of <6.6 kPa and/or oxygen saturation less than 80%) in 85% of the patients, with a median duration of hypoxaemia of four minutes in the pethidine group and 1.5 minutes in the alfentanil group. We observed a total of 50.8% episodes of hypoxia in the 57 attempts. These were short in duration (mean of 17 seconds). Oei *et al*[6] in a randomised trial comparing placebo with atropine, morphine, and suxamethonium noted that the mean lowest saturation was 58% in the placebo group and 60% in the intervention group. Lemyre *et al*[19] compared placebo with morphine, and noted an overall incidence of bradycardia (heart rate less than 90 beats/min) in 94% of cases. We observed three episodes of bradycardia in 57 intubation attempts. These infants were treated and observed with no change in our usual practice. We therefore do not have information on changes in blood pressure during intubation. The changes are in any case very rapid, and require continuous arterial invasive monitoring to document; very few of our infants had an arterial line at the time of intubation.

This observational study was part of a quality improvement initiative undertaken to evaluate our current practices in relation to neonatal intubation. This regimen has been in practice in our NICU for over five years. It is important to highlight that each intubation was supervised by a neonatal fellow or staff familiar with the drugs that were being administered, and also experienced in neonatal intubation. It is essential that personnel are familiar with the potential unwanted side effects associated with these drugs, are able to recognise these potential complications early, and intervene appropriately should the need arise. We have been able to show that most babies can be intubated with good analgesia and with only brief and mild hypoxia, or no hypoxia at all. This was achieved in a teaching environment in which most

What is already known on this topic

- Conscious awake intubation causes adverse physiological responses
- Intravenous premedication for neonatal intubation is not universally used

What this study adds

- This is the first report documenting the use of mivacurium for intubation of the neonate
- Most babies can be intubated with good analgesia and with only brief and mild hypoxia, or no hypoxia at all

trainees had little experience in intubation and were provided with excellent intubation conditions resulting in an overall high success rate.

It is ethically imperative that planned painful procedures are preceded by the administration of analgesic agents. The premedication regimen we have described is highly effective and appears safe. The optimal premedication regimen has, however, not yet been determined; further randomised trials incorporating muscle relaxants are warranted.

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REFERENCES

1 **Shah V**, Ohlsson A. The effectiveness of premedication for endotracheal intubation in mechanically ventilated neonates. A systematic review. *Clin Perinatol* 2002;**29**:535–54.
2 **Whyte S**, Birrell G, Wyllie J. Premedication before intubation in UK neonatal units. *Arch Dis Child Fetal Neonatal Ed* 2000;**82**:F38–41.
3 **Pokela ML**, Koivisto M. Physiological changes, plasma beta-endorphin and cortisol responses to tracheal intubation in neonates. *Acta Paediatrica* 1994;**83**:151–6.
4 **Friesen RH**, Honda AT, Thieme RE. Changes in anterior fontanel pressure in preterm neonates during tracheal intubation. *Anesth Analg* 1987;**66**:874–8.
5 **Duncan H**, Zurick N, Wolf A. Should we reconsider awake neonatal intubation? A review of the evidence and treatment strategies. *Paediatr Anaesth* 2001;**11**:135–145.
6 **Oei J**, Hari R, Butha T, *et al*. Facilitation of neonatal nasotracheal intubation with premedication: a randomized controlled trial. *J Paediatr Child Health* 2002;**38**:146–50.
7 **Bhutada A**, Sahni R, Rastogi S, *et al*. Randomised controlled trial of thiopental for intubation in neonates. *Arch Dis Child Fetal Neonatal Ed* 2000;**82**:F34–7.
8 **Hancock S**, Newell S, Brierley J, *et al*. Premedication for neonatal intubation: current practice in Australia and the United Kingdom. *Arch Dis Child Fetal Neonatal Ed* 2000;**83**:F77.
9 **Goldberg ME**, Larijani GE, Azad SS, *et al*. Comparison of tracheal intubating conditions and neuromuscular blocking profiles after intubating doses of mivacurium chloride or succinylcholine in surgical outpatients. *Anesth Analgesia* 1989;**69**:93–9.
10 **Fernandez CV**, Rees EP. Pain management in Canadian level 3 neonatal intensive care units. *Can Med Assoc J* 1994;**150**:499–504.
11 **Vogel S**, Gibbins S, Simmons B, *et al*. Premedication for endotracheal intubation in neonates: a Canadian perspective [abstract]. *Pediatr Res* 2000;**47**:438A.
12 **McAllister JD**, Gnauck KA. Rapid sequence intubation of the pediatric patient. Fundamentals of practice [review]. *Pediatr Clin North Am* 1999;**46**:1249–84.
13 **Cook DR**, Gronert BJ, Woelfel SK. Comparison of the neuromuscular effects of mivacurium and suxamethonium in infants and children. *Acta Anaesthesiol Scand* 1995;**39**(suppl 106):35–40.
14 **Barrington KJ**, Byrne PJ. Premedication for neonatal intubation. *Am J Perinatol* 1998;**15**:213–16.
15 **Fahnenstich H**, Steffan J, Kau N, *et al*. Fentanyl-induced chest wall rigidity and laryngospasm in preterm and term infants. *Crit Care Med* 2000;**28**:836–9.
16 **Falck AJ**, Escobedo MB, Baillargeon JG, *et al*. Proficiency of pediatric residents in performing neonatal endotracheal intubation. *Pediatrics* 2003;**112**:1242–7.
17 **Konrad C**, Schüpfer G, Wietlisbach M, *et al*. Learning manual skills in anesthesiology: is there a recommended number of cases for anesthetic procedures? *Anesth Analgesia* 1998;**86**:635–9.
18 **Leone TA**, Rich W, Finer NN. Neonatal intubation: success of pediatric trainees. *J Pediatr* 2005;**146**:638–41.
19 **Lemyre B**, Doucette J, Kalyn A, *et al*. Morphine for elective endotracheal intubation in neonates: a randomized trial BMC. *Pediatrics* 2004;**4**:20.